REMARKS

Claims 1-18 are pending in the application. Claims 14-18 have been cancelled by this amendment. Therefore, claims 1-13 are at issue.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

Applicants hereby affirm the election of claims 1-13 (i.e., examiner's Group I). Claims 14-18, drawn to nonelected inventions, have been cancelled, without prejudice to filing a divisional application directed to the subject matter of these claims. Applicants also affirm the election of the compound of claim 13 as the elected species, with traverse.

The present invention provides an article of manufacture for human pharmaceutical use comprising a package insert, a container, and an oral dosage form comprising a PDE5 inhibitor at unit dosages between about 1 mg and about 10 mg/dosage form. The package insert provides a dosing regimen characterized by a chronic administration of the PDE5 inhibitor.

The beneficial effects of a chronic dosing regimen were observed in clinical studies and through the discovery that the administration of a PDE5 inhibitor improves or conditions the vasculature such that the corpus cavernosum smooth muscle tissue responds to therapy at PDE5 inhibitor doses *below* that

required to yield the same response with on-demand or acute therapy.

The present claims are based on detailed experiments and clinical trials, and the unexpected observations that sexual dysfunction can be treated using a chronic, low dose of a PDE5 inhibitor having an IC_{50} value for inhibition of PDE5 less than 10 nM *and* a sufficient bioavailability to be effective in about 1 mg to about 10 mg unit oral dosages. In particular, note the unexpected results set forth in Examples 6 and 7 of the specification.

A chronic dosing regimen of about 1 to about 10 mg of a PDE5 inhibitor for at least three days also provides other benefits including (a) spontaneity in sexual relations, (b) a return to normalcy, i.e., the patient is not required to plan sexual activity around administration of the PDE5 inhibitor, (c) unexpected efficacy for such a low oral dose of PDE5 inhibitor, including an observation of a greater response to the PDE5 inhibitor from a lower chronic PDE5 inhibitor dose than to the currently labeled 25 mg acute, on-demand dose of sildenafil, (d) lower toxicity attributed to a lower dose of PDE5 inhibitor, and (e) no to low adverse effects attributed to the selective PDE5 inhibitor and a low dose.

Overall, it has been demonstrated that chronic dosing of a PDE5 inhibitor having the properties enumerated above provides the same or improved efficacy at about 1 mg to 10 mg than a higher acute on-demand dosage (i.e., at least 25 mg) presently administered. The enhanced efficacy demonstrated by low daily dosing of a PDE5 inhibitor in treating erectile dysfunction is not dependent on drug accumulation, but

rather results from improved vascular responsiveness when the PDE5 inhibitor is present continuously, or essentially continuously, in plasma.

The "vascular conditioning" effect has not been demonstrated previously with PDE5 inhibitors in particular, or PDE inhibitors in general. In particular, vascular conditioning has not been observed in on-demand dosing of a PDE5 inhibitor, or in individuals taking an acute PDE5 inhibitor dose for a short time span. It is expected that vascular conditioning occurs after chronic administration of the PDE5 inhibitor, for example, after about three daily doses of up to 10 mg, preferably after five days of daily dosing, and more preferably after seven days of daily dosing. In addition, after about three days of daily dosing, intermittently missing one chronic dose may lead to a reduction in vascular conditioning, but not a complete loss of conditioning.

It has been theorized that vascular conditioning is caused by a partial or complete reversal of circulatory dysfunctions in penile circulation arising from conditions such as diabetes, atherosclerosis, smoking, hypertension, or a combination of such factors. These conditions result in thickening of the arterial wall, decreased arterial compliance, and decreased responsiveness to endogenous vasodilators, such as nitric oxide.

The presently claimed invention provides unexpected advantages over a currently available pharmaceutical product that utilizes a PDE5 inhibitor, and is marketed under the trademark VIAGRA®. While sildenafil has obtained significant commercial success, problems in the treatment of erectile dysfunction (ED) still

exist. First, ED therapy using sildenafil is based on an on-demand or PRN therapy. "On demand" dosing is an acute administration of a drug for treating erectile dysfunction prior to expected sexual activity. The user, therefore, must plan ahead, and, as presently labeled, ingest a relatively large oral dose (i.e., at least 25 mg) of sildenafil at least one hour prior to engaging in sexual activity. The onset of beneficial effects also may be delayed when sildenafil is administered with a meal.

Second, the relatively large on-demand dose of sildenafil results in significant adverse side effects, including facial flushing (10% incidence rate). Thus, even with the availability of sildenafil, there remains a need for improved pharmaceutical products that are useful and more convenient in treating sexual dysfunction. The present claims are directed to an article of manufacture that meets this unrealized need.

With respect to the restriction requirement, applicants have cancelled nonelected claims 14-18, thereby rendering the restriction moot. With respect to the election of specie requirement, applicants traverse the withdrawal of claim 12 from consideration at this time. The basis of the species election is that an undue burden would be placed on the Patent Office. However, claim 12 specifically recites two additional PDE5 inhibitors, and a search directed to the chronic administration of these two PDE5 inhibitors and the elected specie would not impose a burden on the Patent Office.

In particular, numerous references directed to sildenafil are disclosed in the specification and

applicants' previously filed Invention Disclosure Statement. Also, the examiner cited a vardenafil reference in the present Office Action.

Because search and examination of the elected specie and the species of at least claim 12 can be made without serious burden on the examiner, it would be wasteful of the time, effort, and resources of both the applicants and the Patent Office to prosecute these claims in separate applications. Search and examination of both claims 12 and 13 in a single application would be much more efficient than requiring the Patent Office and applicants to do so in two separate applications. Accordingly, it is submitted that the compounds of claims 12 and 13 should be examined at this time. Reconsideration and withdrawal of the specie requirement with respect to claim 12 is respectfully requested.

Claim 1 has been amended to recite a chronic dosing regimen for at least three days. Support for this amendment can be found in the specification (e.g., page 9, lines 28-32 and page 13, lines 1-6) and in originally filed claim 15.

Claims 5-13 are objected to as being in improper form because the multiple dependent claims do not refer to the claims in the alternative. It is submitted that this amendment overcomes this objection because claims 5-13 have been amended to recite the claims in the alternative. Accordingly, it is submitted that this objection should be withdrawn.

Claims 1-4 stand rejected under the judicially created doctrine of obviousness-type double patenting over various claims of copending U.S. Patent Application No. 09/558,911. Applicants will file a

terminal disclaimer, if the conflicting claims are patented, to overcome this obviousness-type double patenting rejection.

Claims 1-4 stand rejected under 35 U.S.C. §103 as being obvious over WO 96/32003 (WO '003) in view of WO 99/24433 (WO '433). The examiner contends that it would have been obvious to utilize a compound of WO '003 or WO '433 in a container with a package insert, and that it reasonably would have been expected that the treatment of erectile dysfunction, and reduced side effects, would result. In view of the following, it is submitted that this rejection is in error and should be withdrawn.

WO '003 discloses a PDE5 inhibitor capable of treating numerous diseases and conditions, including erectile dysfunction. It should be noted the WO '003 is *not* directed to a PDE5 inhibitor disclosed and claimed in the present application, i.e., compare formula I of WO '003 to structure (I) at page 14 of the present specification, and especially note the ring at the far right-hand side of each structure. Applicants direct the examiner's attention to WO 97/03675 cited in a previously filed Information Disclosure Statement.

The examiner relies upon WO '003 for a teaching of a PDE5 inhibitor having an IC_{50} value less than 10nM, oral administration, and a dosage of 0.5-800mg, in tablets, for administration "once or several times per day." However, WO '003 fails to teach or suggest several of the claimed features.

For example, an IC_{50} value of less than 10nM *alone* is not suitable in accordance with the present invention. The PDE5 inhibitor also must have a sufficient bioavailability to be effective in about 1 to

about 10 mg unit oral dosages. Neither cited reference, nor any other reference of which applicants are aware, teaches or suggests this combination of features.

Furthermore, WO '003 merely teaches a *daily* dosage that can be administered once per day or in multiple doses over the course of a day, i.e., "once or several times *per* day." WO '003 is totally silent with respect to a chronic administration, e.g., daily administration for at least three days, to treat erectile dysfunction. No prior drug for the treatment of erectile dysfunction is used in a chronic dosing regimen at a low dosage of about 1 to about 10 mg, but rather in an "on demand" regimen at a relatively high dosage of at least 25 mg, e.g., VIAGRA®.

WO '433 discloses the PDE5 inhibitor vardenafil. Contrary to the examiner's statement, WO '433 does not disclose sildenafil, which is the subject of patents assigned to Pfizer. In particular, compare the generic structure of WO '433 with the structure of sildenafil and vardenafil at page 17 of the specification, and especially compare the fused bicyclic ring systems. Nevertheless, the WO '433 disclosure, like WO '003, and known sildenafil references, do not teach or suggest a chronic dosing regimen of about 1 to about 10 mg of vardenafil or sildenafil for at least three days to improve vascular conditioning and treat erectile dysfunction.

The present invention relies on the discovery that improved vascular conditioning results from the chronic administration of a PDE5 inhibitor as defined in claim 1(a), for example, and in claim 13 in particular. This improved vascular conditioning is useful

in treating sexual dysfunction. The present claims are both novel and nonobvious over other articles of manufacture for treating erectile dysfunction. In particular, novelty of the present claims does not lie in the mere presence of a container and an insert, but upon the identity of the PDE5 inhibitor, as defined in paragraph (a) of claims 1-4, in the container, *and* upon the *information* in the package insert, i.e., a chronic dosing regimen for treating erectile dysfunction. There is no known article of manufacture, or reference, that teaches or suggests these claimed features.

WO '003 and WO '433 discloses PDE5 inhibitors for treating erectile dysfunction and provide a broad oral dosage range. Neither reference teaches or suggests a chronic dosing regimen of at least three days as presently recited in independent claim 1. WO '003 teaches *dividing* a daily dose into multiple doses, but fails to teach or suggest consecutive daily doses in a low dosage amount. In contrast, present-day PDE5-based treatments for erectile dysfunction rely upon "on demand" administration of a PDE5 inhibitor at a high dosage rate.

The cited references fail to teach or suggest a chronic dosing regimen, and no presently available treatments utilize a chronic dosing regimen. The references, alone or in combination, absolutely fail to provide any motivation for a person skilled in the art to consider a chronic dosing regiment, and provide no incentive for a person skilled in the art to reduce the PDE5 inhibitor dosage rate by at least 60% (e.g., 25 mg down to 1 mg to 10 mg) with any reasonable expectation of providing an article of manufacture useful in the treatment of erectile dysfunction.

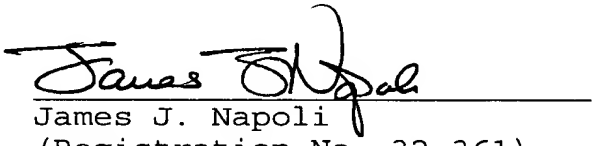
In addition, the presently claimed invention meets an unsatisfied need in the art, i.e., a treatment for erectile dysfunction that permits more normal sexual relations with respect to spontaneity and not having to preplan sexual activity. Accordingly, it is submitted that the rejection of all pending claims as being obvious over WO '003 in view of WO '433 is in error and should be withdrawn.

It is submitted further that the claims are now in proper form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE
Whitaker et al. U.S.S.N. 09/834,442

1. (Amended) An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising a PDE5 inhibitor having an IC_{50} for the inhibition of PDE5 less than 10 nM, and sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizing a chronic dosing regimen <u>for at least three days</u>; and

(c) a container.

5. (Amended) The article of manufacture of [claims 1 through 4] <u>claim 1, 2, 3, or 4</u>, wherein the PDE5 inhibitor further has

(i) at least a 100 fold differential in IC_{50} values for the inhibition of PDE5 versus PDE6, and

(ii) at least 1000 fold differential in IC_{50} values for the inhibition of PDE5 versus PDE1c.

6. (Amended) The article of [claims 1 through 4] <u>claim 1, 2, 3, or 4</u> wherein the oral dosage form comprises about 1 mg, about 2 mg, about 5 mg, or about 10 mg, of the PDE5 inhibitor.

7. (Amended) The article of [claims 1 through 4] <u>claim 1, 2, 3, or 4</u> wherein the chronic dosing regimen is a daily dosing regimen.

8. (Amended) The article of [claims 1 through 4] claim 1, 2, 3, or 4 wherein the chronic dosing regimen comprises administration of about 1 mg/day to about 10 mg/day of the PDE5 inhibitor.

9. (Amended) The article of [claims 1 through 4] claim 1, 2, 3, or 4 wherein the package insert provides a maximum dosage of the PDE5 inhibitor of about 10 mg per day.

10. (Amended) The article of [claims 1 through 4] claim 1, 2, 3, or 4 wherein the PDE5 inhibitor is selected from the group consisting of
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione;
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]-phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsul-phonyl)phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one; and
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

12. (Amended) The article of [claims 1 through 4] claim 1, 2, 3, or 4 wherein the PDE5 inhibitor is selected from the group consisting of sildenafil and vardenafil.

13. (Amended) The article of [claims 1 through 4] claim 1, 2, 3, or 4, wherein the PDE5 inhibitor has the structure